Claim 21, line 4, please delete "at least one non-fibrotic growth factor selected from the group consisting of".

Claim 21, line 5, please delete "and FGF".

REMARKS

Claims 1 and 3-22 are now pending in the application. Claim 2 has been canceled in the foregoing claim amendments.

Applicants' Invention

Applicants' invention relates to the use of non-fibrotic growth factors and fragments, such as TGFβ-3 or FGF or their fragments, to promote wound healing with little or no scarring as compared to natural healing processes. The TGFβ-3 non-fibrotic growth factor or fragments are used in combination with either (1) no fibrotic growth factors, (2) fibrotic growth factors, such as TGFβ-1, TGFβ-2, PDGF, and mixtures of two or more thereof, wherein the fibrotic growth factors are present in a lower proportion than the non-fibrotic growth factor compared to the growth factors present naturally in wounds or disorders in question, or (3) with such fibrotic growth factors together with anti-fibrotic agents against them. These agents are incorporated into a pharmaceutically acceptable carrier.

Applicants have discovered a means to promote healing by using TGFβ-3 or fragments to overcome scarring which would normally occur.

At page 8 through page 15 of the specification, Applicants have included experimental data showing tests individually using TGFβ-1, TGFβ-2 or TGFβ-3.

Additionally, tests were run where antibodies for neutralizing TGFβ-1 (anti-TGFβ-1) and TGFβ-2 (anti-TGFβ-2) were used. Wounds treated with TGFβ-3, anti-TGFβ-1 and anti-TGFβ-2 have less fibronectin and better orientation, than wounds treated with TGFβ-1 or TGFβ-2, which have increased fibronectin with abnormal orientation. Additionally, wounds treated with TGFβ-3 contained a low profile of macrophages, while wounds treated with TGFβ-1 and TGFβ-2 contained a higher profile of macrophages. TGFβ-3 treated wounds develop more blood vessels compared to the control wounds or wounds treated with TGFβ-1 or TGFβ-2. Applicants note that this is a marked effect. Wounds treated with TGFβ-3, anti-TGFβ-1 and anti-TGFβ-2 have collagen having a similar reticular pattern to the surrounding dermis, while wounds treated with TGFβ-1 and TGFβ-2 and the control wounds have abnormal orientation of collagen.

As the data shows, TGFβ-3, unlike TGFβ-1 or TGFβ-2, acts to reduce wound scarring. Additionally, using anti- TGFβ-1 and anti-TGFβ-2 improves wound healing by reducing scarring.

Rejections under 35 U.S.C. §102(b)

Claims 1, 3, 6, 17 and 18 stand rejected under 35 U.S.C. §102(b) as being anticipated by the PCT publication WO 90/03810 (hereafter Geistlich). The rejection states that Geistlich et al teach delayed release compositions for wound healing. The compositions are then dispersed in a hydrogel. The rejection states that mere recitation of newly discovered functional properties, inherently possessed by a composition, does not cause a claim to be distinguished over the prior art.

Geistlich relates to delayed release agents for wound healing, including certain growth factors. Geistlich neither teaches or suggests the use of the TGFβ-3 as a growth factor nor teaches or suggests the use of the TGFβ-3 as a non-fibrotic growth factor.

Applicants' claims 1 and 21 have been amended to claim TGFβ-3 as the non-fibrotic growth factor, used either without fibrotic growth factors or with specific combinations of other components. Geistlich only teaches generalized use of "growth factors" and does not contain any teachings leading to Applicants' claimed limitations. Specifically, Applicants' claims require TGFβ-3 as a non-fibrotic growth factor, either with no fibrotic growth factor or in combination with specific fibrotic growth factors. Such is neither disclosed, nor taught, nor suggested by Geistlich. Geistlich does not contain any teachings to TGFβ-3 as a specific non-fibrotic growth factor together with any of (1) no fibrotic growth factor, (2) fibrotic growth factors at lower concentration that occur naturally, or (3) fibrotic growth factor together with anti-fibrotic agents. Without teaching or suggesting the specific limitations of Applicants' claims, Geistlich cannot anticipate Applicants' claims.

Applicants' claimed compositions are different from those that are naturally occurring, such as those in Geistlich. Applicants are not just claiming a new function, but are claiming a new composition and therefore, submit that Geistlich does not anticipate their claims, drawn to TGFβ-3 with no fibrotic growth factor or with fibrotic growth factors or fragments thereof present in the composition in a lower proportion to TGFβ-3 than occurs naturally in the wounds or disorders in question, or with such fibrotic growth factors together with antibodies selected from the group which neutralize TGFβ-1, TGFβ-2 or PDGF. Since Geistlich et al do not teach or suggest each element of Applicants' claims,

Applicants submit that Geistlich et al neither anticipate nor render obvious their claims. The rejection of Applicants' claims 1, 3, 7-11, 17, 18 and 21 has thus been overcome by Applicants' foregoing amendments of claims 1 and 21. Accordingly, Applicants request withdrawal of the rejection over Geistlich.

Claims 1, 2, 6, 7, 12 and 14-20 stand rejected under 35 U.S.C. §102(b) as anticipated by the EP published application EP 422,225 (hereafter "Cerletti"). The rejection states that Cerletti teaches a method for treating wounds with TGFβ-like proteins. The rejection notes that Cerletti teaches TGFβ-1, TGFβ-2 and TGFβ-3. The rejection states that the TGFβ-like proteins of Cerletti would inherently possess the properties of the compositions of Applicants' claims.

Cerletti relates to a process for producing biologically active, dimeric TGFβ compositions and pharmaceutical compositions comprising the compositions. Cerletti does not teach the use of TGFβ-3 in the specific compositions required by Applicants' claims. Applicants are not claiming a new use for an old compound, but are claiming the non-fibrotic growth factor TGFβ-3 in specific compositions which are different from those that occur naturally. Specifically, Applicants are claiming TGFβ-3 with no fibrotic growth factor or with fibrotic growth factors or fragments thereof present in the composition in a lower proportion to TGFβ-3 than occurs naturally in the wounds or disorders in question, or with such fibrotic growth factors together with antibodies selected from the group which neutralize TGFβ-1, TGFβ-2 or PDGF.

Cerletti discloses many processes for preparing TGFβ-like proteins. However, there is no teaching or suggestion in Cerletti that shows that any particular one of the resulting

proteins are to be used in Applicants' claimed compositions. Applicants have specifically structured their claims so that the non-fibrotic growth factor TGFβ-3 is used with no fibrotic growth factor or in combination with other materials to bring about a composition which is particularly effective in wound healing without scarring. Cerletti does not teach or suggest such combination. Cerletti does not teach or suggest any difference between the different TGFβ proteins. A skilled person would not be motivated to use any particular TGF protein, much less "TGFβ-3 with no fibrotic growth factor or with fibrotic growth factors or \fragments thereof present in the composition in a lower proportion to TGFβ-3 than occurs naturally in the wounds or disorders in question, or with such fibrotic growth factors together with antibodies selected from the group which neutralize TGFβ-1, TGFβ-2 or PDGF." Without teachings of the specific claimed combinations, Cerletti cannot anticipate Applicants' claims.

At pages 21-24, in Examples 6A, 6B and 6C, Cerletti provides experimental procedures and results for testing TGFβ-2. TGFβ-2 is a fibrotic growth factor. Cerletti fails to teach the use of TGFβ-3 in the experiments. Cerletti does not show results for any experiments run with TGFβ-3. Cerletti fails to teach that if the experiments had been performed using TGFβ-3 the results obtained would be the same as were obtained using TGFβ-2. Cerletti fails to teach using "a composition for use in the healing of wounds... comprising TGFβ-3 with no fibrotic growth factor or with fibrotic growth factors or \fragments thereof present in the composition in a lower proportion to TGFβ-3 than occurs naturally in the wounds or disorders in question, or with such fibrotic growth factors together with antibodies selected from the group which neutralize TGFβ-1, TGFβ-2 or

PDGF." Thus, Cerletti does not identically disclose each and every limitation of Applicants' presently claimed compositions.

At pages 25-26, in Examples 7A, 7B, and 7C, Cerletti discloses pharmaceutical compositions in which the active substance is clearly stated to be "TGFβ-like protein." At page 4, line 32, Cerletti defines "TGFβ-like protein" to embrace TGFβ-1, TGFβ-2, and TGFβ-3, as well as a number of other proteins. Thus, Cerletti does not identically disclose each and every limitation of Applicants' presently claimed compositions.

Because Cerletti does not identically disclose each and every limitation of Applicants' presently claimed compositions, the claims of the present application are not anticipated by Cerletti. Furthermore, since Applicants' claims as now amended differ substantially from Cerletti, there is no inherent result in Cerletti which could anticipate Applicants' claims by inherently providing the disclosed reduction in scarring resulting from Applicants' compositions. Therefore, the rejection of Applicants' claims 1, 2, 6, 7, 12 and 14-20 under 35 U.S.C. §102(b) as anticipated by Cerletti et al has been overcome and should be withdrawn. Accordingly, Applicants request withdrawal of the rejection over Cerletti.

35 U.S.C. §112 Rejections

The specification is objected to and claims 4 and 5 are rejected under 35 U.S.C. §112, first paragraph, as failing to provide adequate written support. Specifically, the use of the term "anti-fibrotic agents" is questioned.

Claim 4 has been amended according to the Examiner's suggestion to recite "antibodies which neutralize TGFβ-1, TGFβ-2 and PDGF." Accordingly, Applicants request withdrawal of this rejection.

The specification is objected to and claims 1, 4 and 5 are rejected under 35 U.S.C. §112, first paragraph, as failing to provide adequate written support. Specifically, it is alleged that Applicants have failed to provide any direction for the use of such a composition.

A person of ordinary skill in the art at the time the invention was made would have known how to use such a composition. The above cited EP reference, Cerletti, teaches how to use such a composition. At pages 21-26, Cerletti describes an experimental protocol for use of TGFβ-2, and provide pharmaceutical formulations including a cream, an ointment, and a parenteral solution, for TGFβ-like proteins, each of which include concentrations of the active ingredients. Further, as previously pointed out, Applicants have disclosed concentrations and volumes for experimental injections of the TGFβ proteins, at page 10 of the specification. Applicants' quantities are within the range disclosed by Cerletti. Furthermore, Applicants disclose at page 7 of the specification "administering a pharmaceutically effective amount of TGFβ-3 to a patient in need thereof." A person of ordinary skill in the art would know, at least from Cerletti, how to use Applicants' compositions. Accordingly, Applicants request withdrawal of this rejection.

The specification is objected to and claims 1, 4 and 5 are rejected under 35 U.S.C. §112, first paragraph, as failing to adequately teach how to make and/or use the invention.

Specifically, it is alleged that Applicants have failed to provide direction on how the anti-sense oligonucleotides or ribozymes are to be directed into the cell nucleus in vivo.

Applicants first point out that it is only in claim 5, and not in claims 1 and 4, that the anti-sense oligonucleotides and ribozymes are specifically claimed. Accordingly, withdrawal of the rejection of claims 1 and 4 on this ground is requested.

Applicants traverse the rejection of Claim 5, since the knowledge of how the antisense oligonucleotides or ribozymes would be directed into the cell nucleus in vivo was known in the art prior to the filing date of the priority application. The attached Derwent data on three published PCT applications, WO 90/10448, WO 91/18624 and WO 91/04319, show that how to direct the antisense oligonucleotides or ribozymes into the cell nucleus in vivo would be within the knowledge of a person skilled in the art at the time the priority application was filed. The publication date for each of these PCT applications (90.09.20, 91.12.12, and 91.04.04 respectively) is prior to the filing date of Applicants' priority document (92.03.22). As is shown by each of these references, the use of antisense oligonucleotides and ribozymes, and how these species would be directed into the cell nucleus in vivo was publicly known and available. Accordingly, Applicants request withdrawal of the rejection of claim 5 on this ground.

In view of the amendments to the claims and the above comments, Applicants submit that the claims are now in condition for allowance. In the event any issues remain in the prosecution of this application, Applicants request that the Examiner call the undersigned attorney to expedite allowance of the claims. If any fees are required for the

filing of these papers, Applicants request the Commissioner to charge those fees to deposit account #18-0988.

Respectfully submitted,

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